Can low molecular weight heparin replace unfractionated heparin during peripheral arterial reconstruction? An open label prospective randomized controlled trial

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Objective: **This study was undertaken to evaluate the effect of low molecular weight heparin (LMWH) compared with unfractionated heparin (UFH) on the rate of occlusion and bleeding during peripheral vascular surgery.**
Methods: **The study was an open label, prospective, randomized trial, carried out by 20 Swedish surgical and vascular surgical departments that report to the Swedish Vascular Registry (SWEDVASC). Study subjects included patients undergoing peripheral vascular procedures, except carotid surgery. Of the 849 patients included, 817 were followed up to 30 days. LMWH (40 mg of enoxaparin) or UFH (5000 IU heparin) was given intravenously immediately before clamping. The same formulation in diluted form was used for vascular rinsing. Main outcome measures included patent reconstruction at day 1, perioperative blood loss, and the percentage of patients requiring protamin. Further, 30-day data for mortality, repeat operation, and recurrent occlusion are reported.**
Results: **The mortality rate at 30 days was 2.7%, with no difference between groups. The patency rate at 1 day was 91.2% to 98.4%, depending on diagnosis and type of reconstruction. No difference was recorded between study groups ($0.6 < P < 1.0$). At 30 days the patency rate was 83.1% to 100% ($0.2 < P < .9$). Median blood loss was 350 mL (interquartile range [IQR], 200-800 mL) in the LMWH group and 425 mL (IQR, 200-900 mL) in the UFH group ($P = .02$). Protamin was given to significantly fewer patients in the LMWH group ($P = .001$). LMWH was comparable to UFH during peripheral vascular reconstruction in terms of 1-day and 30-day graft patency, operative blood loss, and hemorrhagic complications. Protamine was required less often after LMWH. In this randomized trial LMWH was as effective as UFH in preventing thrombosis without excess bleeding or hemorrhagic complications. (J Vasc Surg 2004;39: 977-84.)**

It is generally agreed that anticoagulation should be used during peripheral arterial reconstructions to reduce the risk for thrombotic occlusion. Common practice is to use unfractionated heparin (UFH), as either standard or body weight–adjusted dose, immediately before vascular clamping, and also to use diluted UFH to flush the vessels during the procedure.

Low molecular weight heparin (LMWH) is now routine prophylaxis against postoperative deep vein thrombosis, and has to a great extent replaced UFH to treat venous thromboembolism. LMWH is also standard treatment in acute coronary syndromes. The present study was undertaken to find out whether a single dose of LMWH is comparable to a corresponding regimen of UFH to prevent arterial thrombosis during vascular reconstruction and to compare blood loss with use of the two types of anticoagulation. When the study was planned, background information was limited. One small study compared LMWH and UFH during infrainguinal surgery, and found the same incidence of graft occlusion in both groups, and comparable effects on coagulation parameters.[1] Another randomized study conducted during infrainguinal surgery showed a significantly lower rate of graft thrombosis at 10 days with LMWH compared with UFH (8% vs 22%).[2] In a trial evaluating the effect of LMWH versus UFH on postoperative deep venous thrombosis during vascular surgery, a secondary end point was arterial occlusion, which occurred at the same rate in the two groups.[3]

The purpose of the present study was to compare the effects of a fixed dose of either LMWH or UFH just before arterial clamping during infrarenal aortic or leg revascularization on immediate outcome, patency, and bleeding. Secondarily, 30-day outcome is reported.

PATIENTS AND METHODS

Between November 2000 and December 2002, 849 patients (507 men, 342 women), ages 40 to 96 years (median, 74 years) undergoing vascular surgery were included in an open randomized trial, and received either 40 mg of enoxaparin (Klexane; Aventis Pharma, Stockholm, Sweden) intravenously or 5000 IU of UFH (heparin; Leo Pharma, Malmö, Sweden) intravenously, immediately before arterial clamping. A corresponding heparin formulation was used to irrigate the vessels locally. Randomization was performed according to the sealed envelope principle, in blocks of 20 patients per hospital. Twenty hospitals

Supported by Aventis Pharma, Stockholm, Sweden.
Competition of interest: none.
Additional material for this article may be found online at www.mosby.com/jvs.
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0741-5214/$30.00

doi:10.1016/j.jvs.2004.01.033

Table I. Outcome of randomization among 849 patients

	Male	*Female*	*n*	*%*
LMWH	270	176	446	52.5
UFH	237	166	403	47.5
Total	507	342	849	

LMWH, Low molecular weight heparin; *UFH,* unfractionated heparin.

Table II. Preoperative treatment

	LMWH (N = 446)		*UFH (N = 403)*	
	n	*%*	*n*	*%*
Aspirin	441	62.6	393	61.6
LMWH	435	30.1	394	31.2
UFH	432	5.3	388	4.9
Clopidogrel	435	2.1	389	2.8
Dextran	434	1.8	387	1.6

LMWH, Low molecular weight heparin; *UFH,* unfractionated heparin.

Table III. Indication for surgery

	LMWH		*UFH*		
	n	*%*	*n*	*%*	P
Critical limb ischemia	237	53.1	227	56.3	.35
Intermittent claudication	114	25.6	87	21.6	.17
Aortic aneurysm	54	12.1	64	15.9	.11
Other aneurysm	29	6.5	14	3.5	.04
Other indication	21	4.7	14	3.5	.37

LMWH, Low molecular weight heparin; *UFH,* unfractionated heparin.

Table IV. Procedures performed

	LMWH		*UFH*		
	n	*%*	*n*	*%*	P
Bypass (N = 684)	354	79.4	330	81.9	.36
Thromboendarterectomy (N = 119)	71	15.9	48	11.9	.10
Thrombectomy (N = 16)	7	1.6	9	2.2	.48
Other procedures (N = 110)	57	12.8	53	13.2	.87

LMWH, Low molecular weight heparin; *UFH,* unfractionated heparin.

randomized 2 to 115 patients each. All participating centers were members of SWEDVASC (Swedish Vascular Registry; see Appendix).

Patients with the following indications for surgery were included in the study: critical limb ischemia (464 patients), intermittent claudication (201 patients), abdominal aortic aneurysm (118 patients), other aneurysm (43 patients), and other indication (35 patients). Patients undergoing carotid surgery were excluded.

A bypass procedure was performed in 684 patients, thromboendarterectomy in 119 patients, thrombectomy in 16 patients, and other procedures in 110 patients.

Postoperative treatment was given at the discretion of the individual hospital, most commonly aspirin in a dose of 75 mg/d or 160 mg/d, but dextran or LMWH was allowed during the first days after surgery.

The main outcomes measured included patent reconstruction at 1 and 30 days, perioperative blood loss, and injection of protamine to stop bleeding. Preoperative coagulation parameters (activated partial thromboplastin time, international normalized ratio) were recorded, as well as platelet count, which was repeated at day 5 to reveal any possible heparin-induced thrombocytopenia. Ankle blood pressure was measured preoperatively and at 30-day follow-up. The surgeon documented possible thrombi and clots during the procedure, and made a subjective evaluation of the technical outcome of the procedure, that is, "successful," "doubtful," or "evident occlusion."

Peroperative bleeding was calculated according to routine procedure, that is, approximation of the amount of blood in surgical cloths and suction devices. Protamin was given at the discretion of the surgeon, indicating that ongoing bleeding was caused by anticoagulation. Coagulation monitoring was exceptional.

Perioperative assessment of patency was accomplished with flow measurement in 357 patients, and with only pulse palpation and clinical judgment in the remaining patients. Postoperative patency was determined according to principles accepted for SWEDVASC registration, including regular pulse palpation and ankle blood pressure measurements, and if any doubt existed, the investigator usually performed duplex ultrasound scanning. The trial did not specifically ask for the method used.

To ascertain an objective evaluation of possible side effects, all serious adverse events were reported for assessment to a monitor who was not engaged in the trial.

Statistical analysis. The hypothesis was that LMWH is as effective as UFH in preventing arterial occlusion. A power calculation revealed a need for 580 patients to detect a 5% percent difference if positive outcome is set at 90% ($\alpha = 0.05$; $\beta = 0.1$). The intention was, however, to include up to 1000 patients. The study was approved by the Ethics Committee of Lund University, and the Swedish Medical Products Agency.

Intention to treat analysis and per protocol analysis were performed. Median and interquartile range (IQR) were used as summary measures for continuous variables. Data were treated nonparametrically. Comparisons of median values in the two groups were performed with the Mann-Whitney test, and differences in proportions in the two groups were evaluated with the X^2 test. Tables with one or more expected cell counts below five were analyzed with the Fisher exact test. Logistic regression was used to calculate odds ratio in 2×2 tables. Box plots were used to summarize marginal distributions graphically. This type of plot has three elements: the box, the whiskers, and the outliers. The box extends from the lower to the upper quartile, and the line in the box represents the median. Whiskers extend to the most extreme observation in each

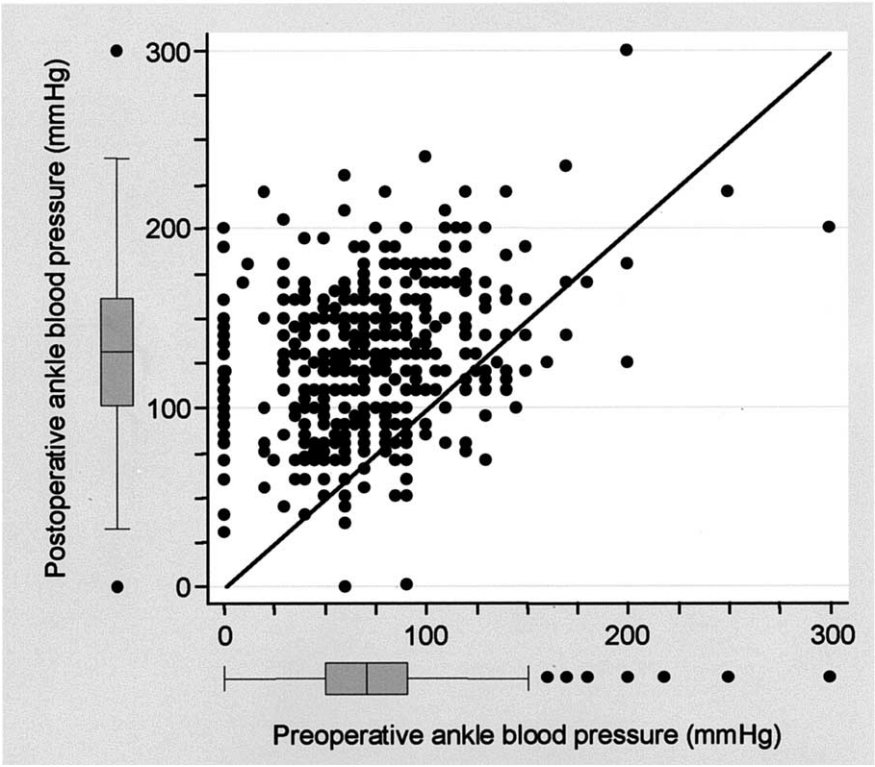

Fig 1. Scatterplot of postoperative versus preoperative ankle blood pressure in 513 legs (aneurysms excluded). Marginal distributions are summarized with box plots.

direction if that value is closer to the median than 1.5 times IQR; otherwise, they extend to 1.5 times IQR. Outliers are defined as observations outside the range of the whiskers, and are presented as individual dots. All tests were two-sided; $P < .05$ was regarded as significant. All statistical calculations were performed with Stata 8.0 (StataCorp, College Station, Tex).

RESULTS

Of the 849 patients, 817 were followed up to day 30. Twenty-three patients (2.7%) died, and nine patients were not followed up for other reasons. The outcome of randomization among the 849 patients is shown in Table I.

There was no difference between the two groups with regard to sex ($P = .6$) (Table I) or age ($P = .9$).

Concomitant preoperative treatment is shown in Table II. The two treatment groups did not differ in this respect.

Coagulation parameters (activated partial thromboplastin time, $P = .3$; international normalized ratio, $P = .2$) and platelet count ($P = .4$) did not differ between the two groups. The indication for surgery (Table III) did not differ except in the small group with "other aneurysms."

Median preoperative ankle blood pressure was 75 mm Hg (IQR, 50-105 mm Hg) in the LMWH group (n = 435) 80 mm Hg (55-120 mm Hg) in the UFH group (n = 370). At 30-day follow-up ankle pressure in the LMWH group (n = 407) had increased, with a median of 55 mm Hg (IQR, 10-85 mm Hg) vs 45 mm Hg (IQR, 10-80) in the UFH group (n = 344). There was no significant difference between the groups ($P = .2$). The change in ankle blood pressure in patients with occlusive disease is illustrated in Fig 1.

The main types of procedures performed are shown in Table IV. "Bypass" includes both autologous and synthetic grafts, all from an aortic tube graft to reconstructions to the crural arteries. The proportion of procedures did not differ between the two study groups.

Perioperative blood loss varied between 0 and 15,000 mL, with a median of 350 mL (IQR, 200-800) in the LMWH group (n = 434) and 425 mL (IQR, 200-900) in the UFH group (n = 389) (Fig 2). This median difference of 75 mL was statistically significant ($P = .02$), although of limited clinical importance. Bleeding of more than 5000 mL was recorded in six patients in the LMWH group and five patients in the UFH group. Blood loss in relation to the procedure and indication for surgery are shown in Tables V and VI (online only), and Figs 3 and 4 (online only).

Five patients received a further 20 to 40 mg of enoxaparin because of prolonged operation. In the UFH group one patient received 2500 IU. Protamin was given to 3% of patients in the LMWH group (n = 440) and 8% in the UFH group (n = 393; $P = .001$). Patients in the LMWH received 10 to 50 mg, and patients in the UFH group

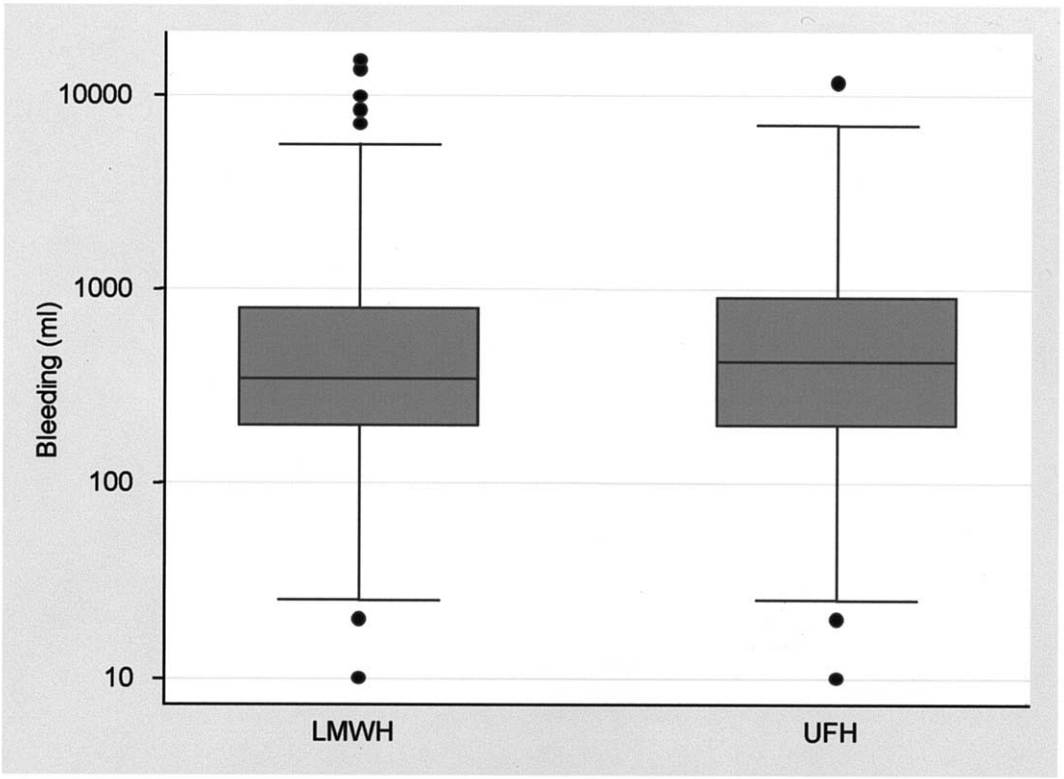

Fig 2. Box plots describe distribution of bleeding in the two randomized groups. Note that the y-axis scale is logarithmic and that 18 bleeding values equal to zero were set to 10 to make logarithmic transformation possible (8 low molecular weight heparin *[LMWH]*, 10 unfractionated heparin *[UFH]*).

received 10 to 80 mg, with the exception of one patient who received 300 mg.

Visible intraoperative thrombosis and clots were recorded in 7% in the LMWH group (n = 440) and in 8% in the UFH group (n = 393; $P = .4$).

The immediate outcome of the procedure was regarded as successful in 91% and 87%, respectively, in the LMWH and UFH groups. An evident occlusion was recorded in three patients in each group.

Repeat operations during the first 24 hours were performed in 68 patients, because of occlusion (n = 26) and bleeding (n = 36), and were equally distributed between the two study groups ($P = .4$). Occlusion occurred in 19 patients in each group (4.3%, LMWH; 4.8%, UFH; $P = .7$). At 30 days 90.8% (LMWH) and 91% (UFH) of reconstructions were patent ($P = .95$). Occlusion between days 2 and 30 occurred in 9.2% of the LMWH group and 9.1% of the UFH group ($P = .95$). Repeat operations during this period were performed in 7.2% in the LMWH group and 6.2% percent in the UFH group ($P = .6$).

Patency data at days 1 and 30 for the respective study groups, according to type of reconstruction, are shown in Table VII. Femoropopliteal reconstructions, distal reconstructions, proximal reconstructions, and extraanatomic reconstructions did not differ at any time point.

Patency with regard to indication for surgery at days 1 and 30 did not differ between the study groups (Table VIII).

At day 5, platelet counts were performed to exclude heparin-induced thrombocytopenia. In the LMWH group (n = 334) the median was 257×10^9/L (IQR, 189-328). In the UFH group (n = 307) corresponding values were 265×10^9/L (IQR, 205-357; $P = .13$). There was no statistically significant difference from preoperative values (Fig 5). Preoperative median value in the entire patient group was 270×10^9/L (IQR, 217-337); 5-day median value was 262×10^9/L (IQR, 196-334). Clinically evident heparin-induced thrombocytopenia was not found. In 11 patients, four in the LMWH group and seven in the UFH group, platelet count was reduced to less than 100×10^9/L, usually subsequent to large perioperative bleeding.

In addition to the above intention-to-treat analysis, a per protocol analysis was performed, without any diverging significance levels.

Complications. Two hundred twenty-one complications were reported during follow-up, 125 in the LMWH group and 96 in the UFH group. Of these complications, 90 occurred in 76 patients and were reported as possible severe adverse events, 42 in the LMWH group and 48 in

Table VII. Patency at 1 and 30 days

	Number of evaluated procedures at 24 hours	*24-hour patency*				*Number of evaluated procedures at 30 days*	*30-day patency*			
			n	*%*	P			*n*	*%*	P
Femoropopliteal reconstruction ak and bk (N = 313)	176	LMWH	169	96.0	.6	174	LMWH	156	89.7	.3
	137	UFH	133	97.1		134	UFH	115	85.8	
Distal reconstruction (N = 170)	79	LMWH	73	92.4	.8	77	LMWH	64	83.1	.4
	91	UFH	83	91.2		87	UFH	76	87.4	
Proximal reconstruction (N = 130)	66	LMWH	64	97.0	1.0*	65	LMWH	60	92.3	.2*
	64	UFH	62	96.9		63	UFH	62	98.4	
Extra-anatomic reconstruction (ax-fem; fem-fem) (N = 62)	28	LMWH	26	92.9	1.0*	28	LMWH	24	85.7	.2*
	34	UFH	32	94.1		33	UFH	32	97.0	

*Fisher exact test.
LMWH, Low molecular weight heparin; *UFH,* unfractionated heparin; *ak,* above knee; *bk,* below knee; *ax-fem,* axillofemoral; *fem-fem,* femorofemoral.

Table VIII. Patency with regard to indication for surgery at 1 and 30 days

	Number of evaluated procedures at 24 hours	*24-hour patency*				*Number of evaluated procedures at 30 days*	*30-day patency*			
			n	*%*	P			*n*	*%*	P
Critical limb ischemia	236	LMWH	223	94.5	0.6	230	LMWH	200	87.0	0.9
	224	UFH	209	93.3		216	UFH	189	87.5	
Intermittent claudication	113	LMWH	109	96.5	1.0*	113	LMWH	106	93.8	0.3
	85	UFH	82	96.5		85	UFH	76	89.4	
Aortic aneurysm	54	LMWH	53	98.1	1.0*	54	LMWH	52	96.3	0.2*
	64	UFH	63	98.4		63	UFH	63	100.0	

*Fisher exact test.
LMWH, Low molecular weight heparin; *UFH,* unfractionated heparin.

the UFH group. Twenty-three patients died, 10 in the LMWH group and 13 in the UFH group.

Bleeding with possible causal relationship to the study drugs was reported in 24 patients given LMWH and 20 given UFH; one patient in each group died. Repeat operation to treat bleeding was performed in 19 patients given LMWH and 17 patients given UFH. In four patients in the UFH group, bleeding was accompanied by myocardial infarction. One spinal hematoma was reported, in a patient in the UFH group who was given epidural anesthesia. The clinical significance of hemorrhage and possible secondary complications was evaluated with a scoring system ranging from 1 (mild) to 5 (fatal). The average severity score was 2.8 in the LMWH group and 3.4 in the UFH group (P = NS). Postoperative bleeding occurred in five patients (three given LMWH, two given UFH) of the 20 patients who were given preoperative treatment with clopidogrel, compared with 39 patients with postoperative bleeding of 790 not given clopidogrel (P = .001; odds ratio 6.4; 95% confidence interval, 2.2-19). Similar comparisons for preoperative treatment with aspirin or LMWH did not disclose significantly increased risk for postoperative bleeding.

DISCUSSION

On the basis that LMWH is effective in prevention of deep venous thrombosis after vascular surgery and after general surgery[4] and that LMWH is useful also to prevent arterial thrombi, both clinically[5] and experimentally,[6] we compared a single dose of LMWH during vascular surgery before vascular clamping with the same regimen using UFH. Further, the better bioavailability and longer plasma half-life of LMWH would be of benefit. Only a few prospective, randomized studies have compared LMWH and UFH in this regard. In the study by Samama et al,[2] 201 patients were randomized to receive either an intravenous bolus dose of LMWH or UFH at a dose related to body weight. This regimen was continued postoperatively, and graft patency was assessed at 10 days. Graft thrombosis occurred significantly less often in the LMWH group (8% vs 22%). Hingorani et al[7] retrospectively analyzed 330 patients receiving either UFH plus warfarin or subcutaneous LMWH plus warfarin. They concluded that use of LMWH is safe, and in this series it also reduced the postoperative length of stay, compared with the UFH group. Paramo et al[8] reported a prospective study of a small group of patients, and found an extremely low rate of graft thrombosis (0% in the LMWH group, 4% in the UFH group, occurring only in femorodistal bypass procedures).

The present study is the only one evaluating in a larger group of patients whether LMWH can be used instead of UFH during surgery. Ninety-five percent of patients randomized in this study were followed up at 30 days. Mortality at 30 days was low, although critical ischemia was the indication for surgery in almost 60% of patients. Nonavail-

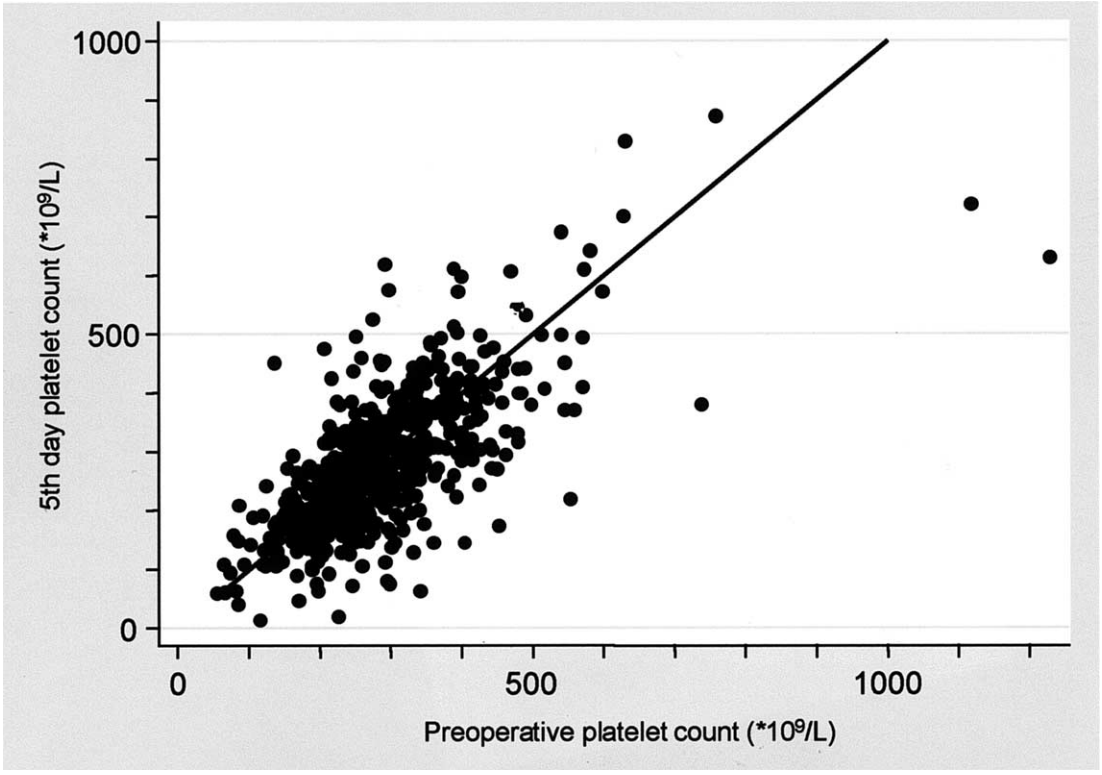

Fig 5. Scatterplot of day 5 platelet count versus preoperative platelet count (n = 618).

able data in this series was 2.5% to 8% for demographic data, ankle blood pressure, bleeding, and occlusion rates at inclusion and to 24 hours of follow-up. At 30 days ankle blood pressure measurements were missing in 12%, and occlusion rates in 5%. The platelet count at 5 days was recorded for about 75% of patients.

The outcome at 30-day follow-up depended not only on the antithrombotic regimen during surgery but also on the postoperative treatment, which may have differed between centers. The study did not record this treatment, but the variation between Swedish vascular centers is limited, and it is likely that most patients received LMWH in the first postoperative days, and subsequently aspirin in a dose of 75 to 160 mg/d. Conclusions regarding the 30-day outcome are therefore secondary in this trial. The immediate outcome regarding occlusion and bleeding is, however, an effect of the perioperative regimen. The two groups were comparable with regard to patient demographic data, indications for surgery, and procedures performed. In the first 24 hours the rate of occlusion did not differ, either in the entire treatment group or when analyzed according to surgical procedures or indications. Blood loss during surgery was slightly less in the LMWH group. The median difference of 75 mL was statistically significant, but the clinical benefit was less important. Outliers, bleeding more than 5000 mL, did not differ between groups. Protamin was administered in significantly fewer patients in the LMWH group. As appears, protamin was used to a limited extent, which is customary in Sweden. Only small doses are given, and only when the surgeon finds that ongoing bleeding may depend on the anticoagulant given. The finding is, however, interesting, because it emphasizes that the role of protamin is limited when anticoagulation is accomplished with LMWH. We compared 5000 IU of UFH and 40 mg of enoxaparin, which seemed to be equipotent according to effect. In a dose-finding study, Kujath et al[9] evaluated four dose regimens, and found that half of the therapeutic dose of reviparin was effective and caused less bleeding. We selected the "higher" prophylactic dose (40 mg) of enoxaparin, and achieved comparable results. It is important to state that various LMWH formulations may differ in some respects.

At 30 days there were no differences between the study groups with regard to the indications for surgery or the procedures performed.

Our results differ from those of Samama et al,[2] achieving significantly fewer occlusions after 10 days in the LMWH group. Their study design differed, however, in that they used LMWH versus UFH daily after surgery until day 10. Furthermore, only femorodistal reconstructions were included. In contrast, the study by Farkas et al[3] reported the same rate of occlusion in the LMWH and UFH groups at 7 to 10 days postoperative.

The clinical significance of the reported hemorrhagic complications in our series did not differ between groups. Only one spinal hematoma was noted in the entire series, in

a patient in the UFH group. Inasmuch as the protocol did not consider the type of anesthesia used, there is no information on the rate of epidural versus general anesthesia.

The combination of preoperative clopidogrel and UFH or LMWH appears to induce a significant risk for postoperative bleeding.

Clinically evident heparin-induced thrombocytopenia was not recorded in any of the 641 patients examined at day 5. In a series of 665 patients, half of whom received UFH and half LMWH as prophylaxis after hip surgery, thrombocytopenia occurred in 2.7% of patients given UFH, but in no patient given LMWH.[10] Blood sampling in this trial was performed from day 5 of heparin prophylaxis. The obvious difference between the two series is the short-lasting heparin treatment in our trial. Our study compares platelet count preoperatively and 5 days postoperatively, which implies that patients with thrombocytopenia induced by perioperative bleeding without any relation to the administration of heparin are recorded.

From a practical point of view, hospitals may benefit from using LMWH for all indications when heparin is required. Taking into consideration that LMWH has replaced UFH for the treatment of deep venous thrombosis and pulmonary embolism, and that it is frequently used postoperatively after vascular procedures, the use of this substance also during vascular surgery seems relevant.

The issue of cost may be mentioned. List prices indicate that LMWH is more expensive, but commonly bulk prices exist for purchase of large volumes and other drugs from the same manufacturer. Although it is likely that UFH may be slightly less expensive than LMWH, calculated from direct costs, indirect costs may increase if UFH must be stored for only a single indication. The value of using a better defined drug with predictable effects should also be considered.

In conclusion, enoxaparin is safe and easy to use, and adequately prevents early thrombotic occlusions. It should be emphasized that this study evaluated only enoxaparin, and it is not possible to conclude that all LMWHs exert the same effect, although this may well be the case.

We thank Janet Johansson, Secretary at the Trial Office, for efficient handling of communication and for support of the trialists.

APPENDIX: SWEDISH ENOXAVASC STUDY GROUP

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Submitted Nov 4, 2003; accepted Jan 26, 2004.
Available online Mar 10, 2004.

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